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Traveling wave solutions of contact-inhibition model of cells ¹

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1 Introduction

In Bertsch-DalPasso-Mimura [3] a mathematical model for two cell populations with *contact-inhibition* ([1], [15]) is proposed. Under a suitable rescaling, it is given by the following parabolic system

$$\begin{cases} u_t = \operatorname{div}(u\nabla(u+v)) + (1-(u+v))u, & \text{in } \mathbf{R}^N \times (0, \infty), \\ v_t = d \operatorname{div}(v\nabla(u+v)) + \gamma \left(1 - \frac{u+v}{k}\right)v, & \text{in } \mathbf{R}^N \times (0, \infty), \end{cases} \quad (1.1)$$

where d, γ and k are positive numbers. Unknown functions $u(x, t)$ and $v(x, t)$ represents the densities of *normal* and *abnormal* cells. The system (1.1) can be regarded as a simplified tumor growth model by Chaplain-Graziano-Presiozi [8], which describes an interaction between normal/abnormal cells, extra cellular matrix generated by normal/abnormal cells, and matrix degrading enzyme. See also Sherratt [14].

In the absence of v , the first equation of (1.1) is simply reduced to

$$u_t = \operatorname{div}(u\nabla u) + (1-v)v, \quad (1.2)$$

which is called the nonlinear degenerate Fisher-KPP equation ([2], [13] and [12], for instance). If the initial function $u(x, 0)$ to (1.2) possesses a compact support in space, the support of the solution $u(x, t)$ of (1.3) satisfying $0 \leq u(x, 0) \leq 1$ expands with finite propagation. Similarly, this property holds for the equation for v in the absence of u

$$v_t = d \operatorname{div}(v\nabla v) + \gamma \left(1 - \frac{v}{k}\right)v. \quad (1.3)$$

The existence of solutions of (1.1) in the framework of weak form and free boundary problem are discussed in [3] and Bertsch-Hilhorst-Izuhara-Mimura [4]. In the case $N = 1$ numerical simulations of the initial-boundary value problem to (1.1) (with a large spatial domain) shows us the effect of contact-inhibition in macroscopic sense. Suppose that the initial functions $u(x, 0)$ and $v(x, 0)$ are compactly supported and that their support are segregated each other. In an initial stage of the simulation, u and v are governed by (1.2) and (1.3) respectively; they behave independently each other. After their supports contact with a point, the supports keep segregated along a new interface. Then u and v are discontinuous at the interfaces. Moreover, u and v behave like traveling wave with a

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constant velocity, and eventually they tends to 0 and k respectively. (Figs. 1 and 2). In particular, it seems that $k > 1$ implies that (u, v) tends to $(0, k)$ as $t \rightarrow \infty$. That is, the abnormal cells occupy the whole region.

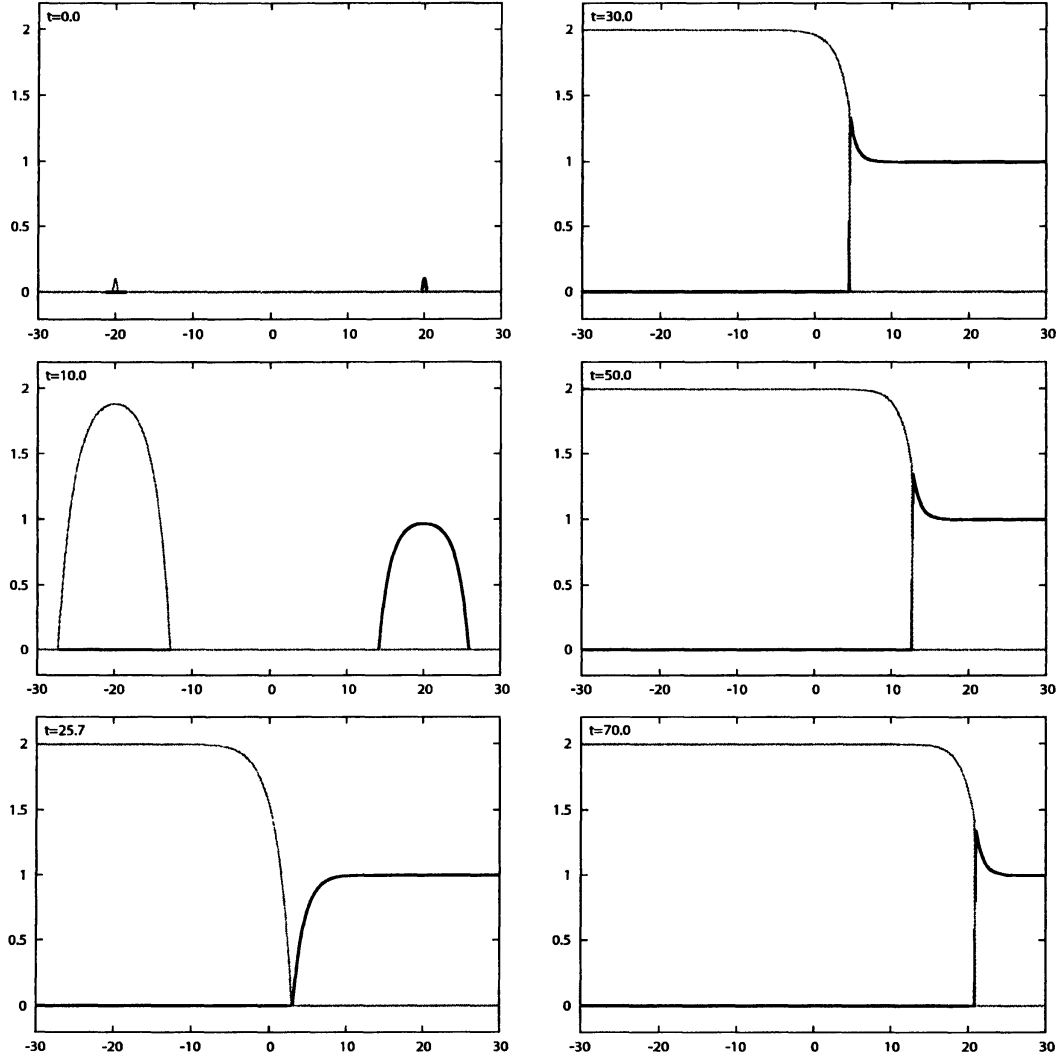


Figure 1: A numerical result for the initial-boundary value problem of (1.1) (with the homogeneous Neumann boundary condition): $d = 1$, $\gamma = 1$, $k = 2$.

The above numerical simulation suggests that it is important to consider (segregated) traveling wave solutions in order to understand the qualitative behavior of solutions of (1.1). To do this, let us introduce the kinetic ODE system of (1.1)

$$\begin{cases} u_t = (1 - (u + v))u, & \text{in } (0, \infty), \\ v_t = \gamma \left(1 - \frac{u + v}{k}\right) v, & \text{in } (0, \infty), \end{cases} \quad (1.4)$$

It is so called competition system of Lotka-Volterra type. Assume $k \neq 1$. Then the

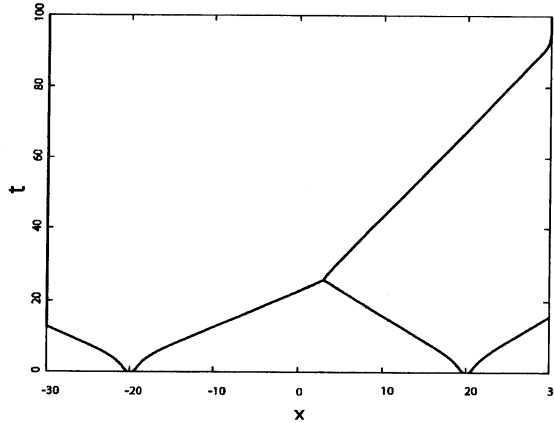


Figure 2: Numerical interfaces arising in Figure 1.1 in (x, t) - space.

equilibrium points are given by $(0, 0)$, $(1, 0)$, $(0, k)$, and their stability is determined by k . If $k > 1$, then $(0, k)$ is globally stable and the other are unstable, and if $0 < k < 1$, then $(1, 0)$ is globally stable and the other are unstable. We remark that (1.4) is monostable system if $k \neq 1$.

The observation on (1.4) formally justify the numerical simulation above. In the case $k > 1$, $(0, k)$ is stable state and $(1, 0)$ is unstable state. Then the traveling wave solution connecting between $(0, k)$ and $(1, 0)$ may appear with a positive velocity. While (1.1) possesses the effect of nonlinear diffusion, this conjecture is true in the case of some semilinear parabolic systems. In addition, it is also expected that (1.1) possesses one parameter family of traveling wave solutions since (1.4) is monostable system.

In this article, we would like to introduce the structure of traveling wave solutions for (1.1). In particular, we will give some mathematical and numerical results for traveling wave solutions of (1.1), which are obtained in [5] and [6].

2 Main results

Suppose $N = 1$. Let us consider the traveling wave solution $(u, v) = (U(x - ct), V(x - ct))$ with velocity c of (1.1). Fix $c \in \mathbf{R}$ arbitrarily, and set the moving coordinate $z = x - ct$. Taking an account of the nonnegativity of the boundary conditions, we are led to

$$\begin{cases} (U(U + V)')' + cU' + U(1 - U - V) = 0 & \text{in } \mathbf{R}, \\ d(V(U + V)')' + cV' + \gamma V \left(1 - \frac{U + V}{k}\right) = 0 & \text{in } \mathbf{R}, \\ (U, V)(-\infty) = (0, k), \quad (U, V)(\infty) = (1, 0), \\ U(z) \geq 0, \quad V(z) \geq 0 & \text{in } \mathbf{R}. \end{cases} \quad (2.1)$$

The boundary conditions at $z = \pm\infty$ comes from (stable and unstable) equilibrium points of (1.4),

We also consider the semi-trivial traveling wave solution $(U, 0)$ and $(0, V)$, which cor-

respond to the traveling wave solutions of (1.2) and (1.3):

$$\begin{cases} (UU')' + cU' + (1 - U)U = 0, & \text{in } (-\infty, \infty), \\ U(z) \geq 0, & \text{in } (-\infty, \infty), \\ U(-\infty) = 0, \quad U(\infty) = 1, \end{cases} \quad (2.2)$$

$$\begin{cases} d(VV')' + cV' + \gamma \left(1 - \frac{V}{k}\right) V = 0, & \text{in } (-\infty, \infty), \\ V(z) \geq 0, & \text{in } (-\infty, \infty), \\ V(-\infty) = k, \quad V(\infty) = 0. \end{cases} \quad (2.3)$$

The monostability of the degenerate Fisher-KPP equations leads us to the existence of one parameter family of traveling wave solutions.

Proposition 2.1 (Aronson [2]). *Let $d > 0$, $\gamma > 0$ and $k > 0$.*

- (i) *There exists a unique $c_* < 0$ such that (2.2) has (weak) solution $U(z)$ if and only if $c \leq c_*$.*
- (ii) *There exists a unique $c^* = c^*(d, \gamma, k) > 0$ such that (2.3) has (weak) solution $V(z)$ if and only if $c \geq c^*$.*

Remark 2.1. The minimal velocity c_* and c^* of (2.2) and (2.3) is characterized by the concept of *sharp* traveling wave solutions. The sharp traveling wave profile V satisfies (2.3) in the following sense:

$$\begin{cases} d(VV')' + c^*V' + \gamma \left(1 - \frac{V}{k}\right) V = 0, & \text{in } (-\infty, 0), \\ V(z) > 0 \text{ in } (-\infty, 0), \quad V(z) = 0 \text{ in } [0, +\infty), \\ V(-\infty) = k, \quad V(0^-) = 0, \\ dV_z(0^-) = -c^*. \end{cases}$$

Indeed,

$$V(z) = k \left[1 - \exp \left(\sqrt{\frac{\gamma}{2dk}} z \right) \right]_+ \quad \text{and} \quad c^* = \sqrt{\frac{d\gamma k}{2}}.$$

On the other hand, if $c > c^*$, then the traveling wave solution is smooth, positive and monotone decreasing with respect to z . The same characterization holds for the weak solution of (2.2) with $c < c_*$ (by a reflection $z \mapsto -z$, we see $c_* = -c^*(1, 1)$). For the similar results on the degenerate Fisher-KPP equations with more general degenerate diffusion, see [13] (and [6]). The stability of traveling wave solutions are discussed in [7], [11] and [12]. See also [10].

We first give the results on the segregated traveling wave solutions of (1.1) for any positive d , γ and k .

Theorem 1 (Segregated traveling wave solutions [6]). *Let d, γ and k be positive constants. Then there exists a unique $c_0 = c_0(d\gamma, k)$ and $h_0 = h_0(c_0)$ such that (2.1) has the unique weak solution (U, V) in the following sense:*

$$\begin{cases} (UU')' + c_0 U' + (1 - U)U = 0 & \text{in } (0, \infty) \\ U(0^+) = h_0, \quad U'(0^+) = -c_0 \\ U(\infty) = 1, \quad U > 0 \text{ in } (0, \infty), \end{cases} \quad (2.4)$$

$$\begin{cases} (VV')' + c_0 V' + \gamma \left(1 - \frac{V}{k}\right) V = 0 & \text{in } (-\infty, 0) \\ V(0^-) = h_0, \quad dV_z(0^-) = -c_0 \\ V(-\infty) = k, \quad V > 0 \text{ in } (-\infty, 0). \end{cases} \quad (2.5)$$

Moreover,

- (i) $c_* < c_0 < c^*$, where c^* and c_* are defined by (i) and (ii) of Proposition 2.1;
- (ii) $c_0 > 0$ if $k > 1$, $c_0 < 0$ if $0 < k < 1$ and $c = 0$ if $k = 1$.

Theorem 1 shows us that k determine the propagation of the segregated traveling wave solution. Moreover, this is consistent with the numerical result shown in the introduction.

Now we assume $d = 1$ and $k > 1$. For one parameter family of traveling wave solutions of (1.1) due to the monostability of (1.4), we have a partial result: it assures the existence of traveling wave solution for $c > c_0$.

Theorem 2 (Overlapping traveling wave solutions [5]). *Consider (2.1) with $d = 1$ and $k > 1$. Let $c_0 > 0$ be the speed of the segregated traveling wave. Then for any $c > c_0$ problem (2.1) has a smooth solution (U_c, V_c) satisfying*

$$U_c(z) > 0, \quad V_c(z) > 0, \quad -c < (U_c + V_c)'(z) < 0 \quad \text{for all } z.$$

Theorems 1 and 2 suggest that the monostable kinetic system provide the structure of traveling wave solutions of (1.1). A numerical results on segregated and overlapping traveling wave solutions are displayed in Fig. 3.

3 Sketch of Proofs

In this section we will give a sketch of proofs for Theorems 1 and 2. Here we always assume that $d = 1$ for simplicity.

3.1 Sketch of proofs of Theorem 1

We begin with the basic proposition for positivity of c when $k > 1$ (and negativity of c when $0 < k < 1$, respectively). Suppose that U and V of (2.4) and (2.5) exist for some $c \in \mathbf{R}$ and $h > 0$. Then U and V can be obtained independently by solving (2.4) and (2.5). A standard argument shows us the following proposition.

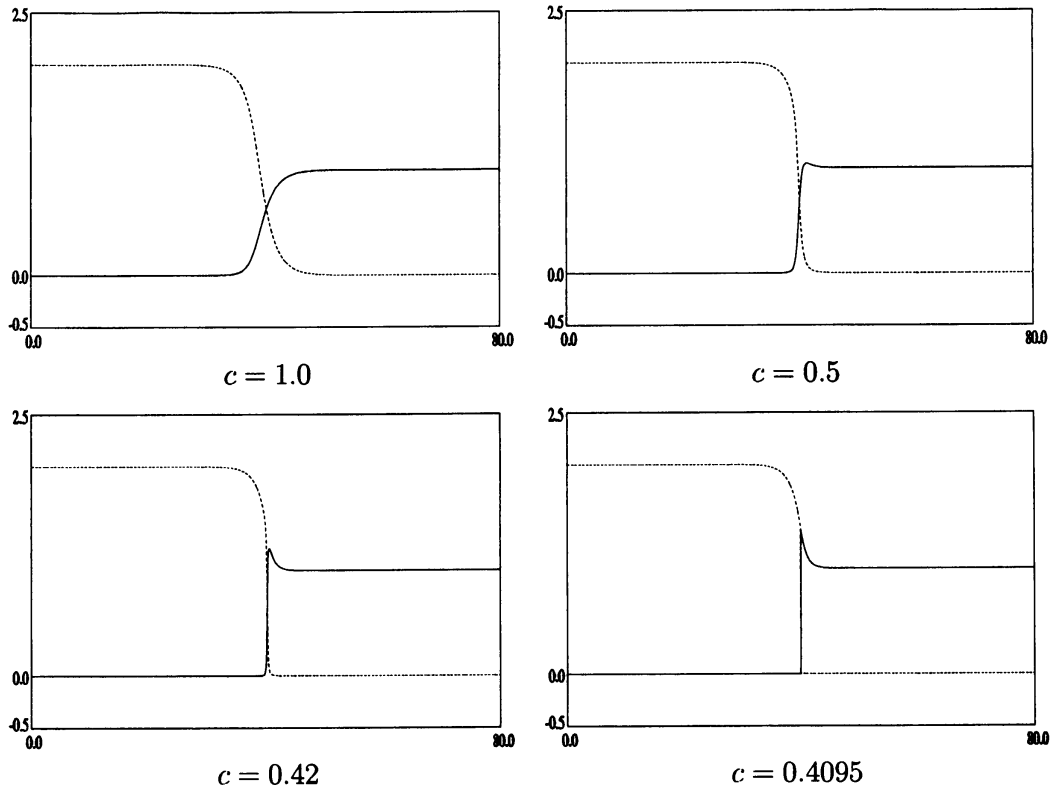


Figure 3: Profiles of overlapping traveling wave solution of (1.1) for each speed $c > c_0$. The solid and dashed curves in the figures mean u and v , respectively. The parameter values are $d = 1$, $k = 2$ and $\gamma = 1$, where the speed of segregated traveling wave solution is $c_0 = 0.4094 \dots$.

Proposition 3.1. *Assume that there exists a pair $(U(z), V(z), h, c)$ satisfying (2.4) and (2.5) for some γ , $k > 0$. Then, the following properties hold true:*

- (i) *If $k > 1$, then $h \in (1, k)$, $U_z < 0$, $V_z < 0$ and $c > 0$.*
- (ii) *If $0 < k < 1$, then $h \in (k, 1)$, $U_z > 0$, $V_z > 0$ and $c < 0$.*
- (iii) *If $k = 1$, then $(U(z), V(z), h, c) = (1, 1, 1, 0)$.*

From now we focus on only the case that $k > 1$ and $c > 0$. In the case $0 < k < 1$ with $c < 0$ Theorem 1 can be proved in similarly. Also, in the case $k = 1$ the proof of Theorem 1 can be easily done. Let us consider the equation

$$(\varphi\varphi_z)_z + c\varphi_z + \gamma f\left(\frac{\varphi}{k}\right)\varphi = 0, \quad (3.1)$$

where $f(s) = 1 - s$. Additionally, set

$$\psi(z) := \frac{\varphi_z(z)}{c}$$

for any solution of (3.1). Then (3.1) defines a dynamical system for $(\varphi(z), \psi(z))$

$$\frac{d}{dz} \begin{bmatrix} \varphi \\ \psi \end{bmatrix} = \begin{bmatrix} c\psi \\ -\frac{1}{c\varphi} \left(c^2\psi(1+\psi) + \gamma\varphi f\left(\frac{\varphi}{k}\right) \right) \end{bmatrix}. \quad (3.2)$$

The following Lemmas 3.1-3.4 are proved.

Lemma 3.1. *Suppose $k > 1$ and $\gamma > 0$. If $0 < c < c^+$, there exist a unique solution $(\varphi, \psi, h) = (\varphi_{k,\gamma,c}^+(z), \psi_{k,\gamma,c}^+(z), h_{k,\gamma,c}^+)$ of (3.2) and*

$$\begin{bmatrix} \varphi(+\infty) \\ \psi(+\infty) \end{bmatrix} = \begin{bmatrix} k \\ 0 \end{bmatrix}, \quad \begin{bmatrix} \varphi(0) \\ \psi(0) \end{bmatrix} = \begin{bmatrix} h \\ -1 \end{bmatrix}. \quad (3.3)$$

Lemma 3.2. *Assume Lemma 3.1 holds. Define the function $h_{k,\gamma}^+ : (0, +\infty) \rightarrow (k, +\infty)$ by*

$$h_{k,\gamma}^+(c) := h_{k,\gamma,c}^+.$$

Then, $h_{k,\gamma}^+$ is continuous and monotone increasing with respect to $c \in (0, +\infty)$. Moreover, $\lim_{c \rightarrow 0} h_{k,\gamma}^+(c) = k$ and $\lim_{c \rightarrow \infty} h_{k,\gamma}^+(c) = +\infty$.

Lemma 3.3. *Suppose the same assumptions as the one in Lemma 3.1. Let $c^* = c^*(k, \gamma) > 0$ be the number as in Proposition 2.1. Then the following (i) and (ii) hold:*

(i) *if $0 < c < c^*$, there exists a unique solution $(\varphi, \psi, h) = (\varphi_{k,\gamma,c}^-(z), \psi_{k,\gamma,c}^-(z), h_{k,\gamma,c}^-)$ of (3.2) and*

$$\begin{bmatrix} \varphi(-\infty) \\ \psi(-\infty) \end{bmatrix} = \begin{bmatrix} k \\ 0 \end{bmatrix}, \quad \begin{bmatrix} \varphi(0) \\ \psi(0) \end{bmatrix} = \begin{bmatrix} h \\ -1 \end{bmatrix}. \quad (3.4)$$

(ii) *if $c \geq c^*$, then for any $h > 0$, there exists no solution of (3.2) and (3.4).*

Lemma 3.4. *Assume Lemma 3.3 holds. Define the function $h_{k,\gamma}^- : (0, c^*) \rightarrow (0, k)$ by*

$$h_{k,\gamma}^-(c) := h_{k,\gamma,c}^-.$$

Then, $h_{k,\gamma}^-$ is continuous and monotone decreasing with respect to $c \in (0, c^)$. Moreover, $\lim_{c \rightarrow 0} h_{k,\gamma}^-(c) = k$ and $\lim_{c \rightarrow c^*} h_{k,\gamma}^-(c) = 0$.*

Lemmas 3.1-3.4 are proved by a standard phase plane method with use of linearizations and invariant manifolds (see Fig. 4). Note that (3.2) admit a singularity at $\psi = 0$. To remove the singularity, we apply the regularization by Aronson [2] to (3.2). Set $\tilde{\varphi}(\tau) := \varphi(z^{-1}(\tau))$, $\tilde{\psi}(\tau) := \psi(z^{-1}(\tau))$ where

$$\tau(z) = \int_0^z \frac{1}{\sigma\varphi(s)\chi'(\varphi(s))} ds.$$

Then, we obtain

$$\frac{d}{d\tau} \begin{bmatrix} \tilde{\varphi} \\ \tilde{\psi} \end{bmatrix} = \begin{bmatrix} c^2\tilde{\varphi}\tilde{\psi} \\ -c^2\tilde{\psi}(1+\tilde{\psi}) - \gamma\tilde{\varphi}f\left(\frac{\tilde{\varphi}}{k}\right) \end{bmatrix}. \quad (3.5)$$

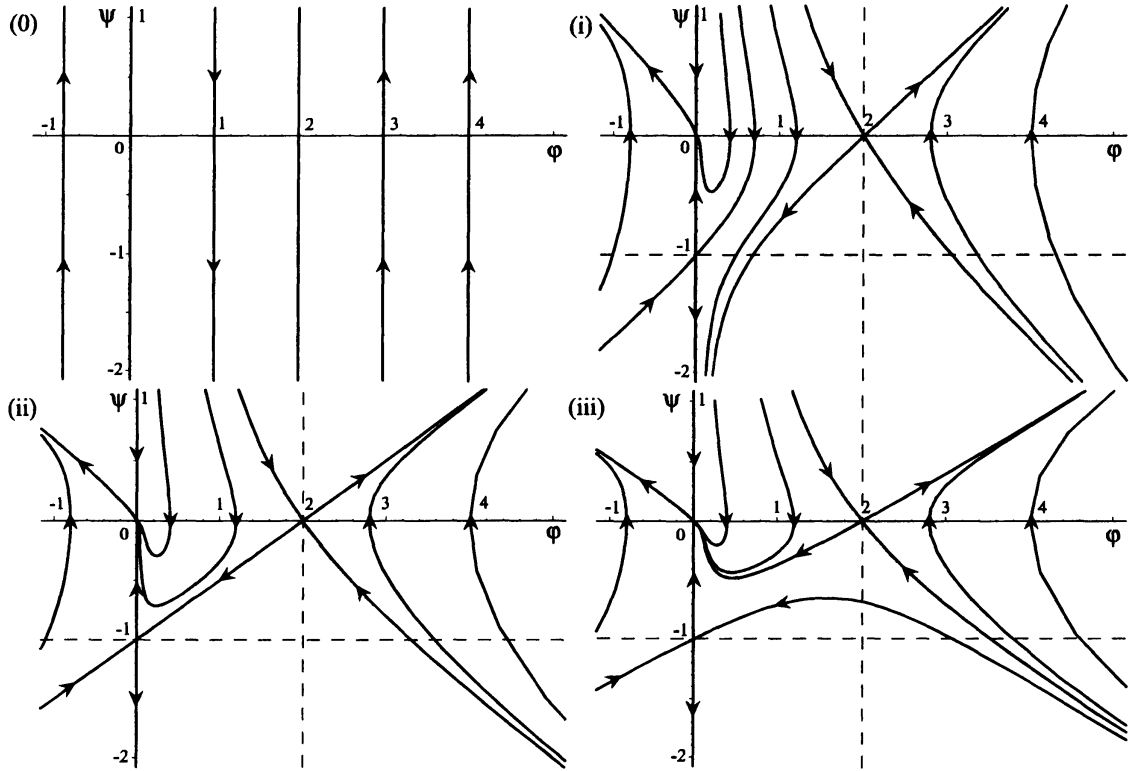


Figure 4: (φ, ψ) -phase planes for (3.5) with $\chi(s) = s$, $\gamma = 1$, $k = 2$: (0) $c = 0$, (i) $c = 0.8(< c^*)$, (ii) $c = 1(= c^*)$, (iii) $c = 1.2(> c^*)$.

Proof of Theorem 1. We only prove the case $k > 1$; so that c should be positive by Proposition 3.1. By Lemma 3.1, there exists a unique $(\varphi_{1,1,c}^+(z), \psi_{1,1,c}^+(z))$ of (3.2) and (3.3) for $c > 0$. Similarly, it follows from Lemma 3.3 that there exists a unique $(\varphi_{k,\gamma,c}^-(z), \psi_{k,\gamma,c}^-(z))$ of (3.2) and (3.4), if and only if $c \in (0, c^*(k, \gamma))$.

From Lemmas 3.2 and 3.4, the intermediate theorem for continuous functions leads us to that the equation

$$h_{1,1}^+(c) = h_{k/\alpha, d\gamma}^-(c)$$

has a unique solution $c_0 = c_0(k, \gamma) \in (0, c^*(k, \gamma))$. Therefore,

$$(U(z), V(z), c) = (\varphi_{1,1,c_0}^+(z), \varphi_{k,\gamma,c_0}^-(z), c_0)$$

is a desired solution of (2.4) and (2.5) with $h_0 = h_{1,1}^+(c_0) = h_{k,\gamma}^-(c_0)$.

Thus, we arrive at the complete proof. \square

3.2 Sketch of proof of Theorem 2

In this subsection we give a sketch of prove Theorem 2. For $(U(z), V(z), c)$ of (2.1), set

$$W = U + V, \quad R = W \left(\frac{W'}{c} + 1 \right), \quad q = v \left(\frac{W'}{c} + 1 \right).$$

Then,

$$U = \frac{W(R-q)}{R} \quad \text{and} \quad V = \frac{Wq}{R}.$$

and we obtain from (2.1) that

$$\begin{cases} R' = \frac{W}{c} \left(W - 1 - \left(W - 1 + \frac{\gamma}{k}(k - W) \right) \frac{q}{R} \right) & \text{for } z \in \mathbf{R} \\ q' = -\frac{\gamma W(k - W)q}{kcR} & \text{for } z \in \mathbf{R} \\ W' = -\frac{c}{W}(W - R) & \text{for } z \in \mathbf{R} \\ R(\infty) = W(\infty) = 1, \quad q(\infty) = 0 \\ R(-\infty) = q(-\infty) = w(-\infty) = k. \end{cases} \quad (3.6)$$

The proof consists of three steps:

- linearization of the system for $R(z)$, $q(z)$ and $W(z)$ near $z = \infty$;
- introduction of W as an independent variable;
- a topological argument applied to the system for $R(W)$ and $q(W)$.

In Figures 5, 6 we have drawn the typical local phase portraits in the (R, W) and the (q, W) -planes.

From Linearization of (2.1) around $(R, q, W) = (1, 0, 1)$, we can use W as an independent variable: as long as $W' \neq 0$, the curves in the 2-dimensional phase portraits correspond to a 1-parameter family of local solutions $(R_\eta(W), q_\eta(W))$ with $\eta \in [0, 1]$, of the singular initial value problem

$$\begin{cases} R_W = \frac{-kW^2(W-1)R + W^2(k(W-1) + \gamma(k-W))q}{c^2kR(W-R)} \\ q_W = \frac{\gamma W^2(k-W)q}{c^2kR(W-R)} \\ R(1) = 1, \quad q(1) = 0. \end{cases} \quad (3.7)$$

We define that $W_\eta \in (0, k]$ is the maximal number such that the local solution $(R_\eta(W), q_\eta(W))$ is defined in $W \in [0, W_\eta]$.

We summarize the results on from a phase space argument for (3.6) together with some invariant manifolds.

Lemma 3.5. *There exists a 1-parameter family $\{(R_\eta(W), q_\eta(W)); \eta \in [0, 1]\}$ of local solutions of problem (3.2) defined on a maximal interval $[1, W_\eta] \subseteq [1, k]$ such that*

- (i) $q_0 = 0$ and R_0 is decreasing and positive in $(1, w_0)$, and $R_0(W) \rightarrow 0$ as $W \rightarrow W_0^-$ if $w_0 < k$;
- (ii) $0 < q_1 < R_1 < 1$ in $(1, w_1)$, $w_1 < k$, and $R_1(W) \rightarrow W_1$ as $W \rightarrow W_1^-$;
- (iii) if $\eta \in (0, 1)$, then $0 < q_\eta < R_\eta < w$, q_η is increasing in $(1, W_\eta)$, and $R_\eta(w) - W \rightarrow 0$ as $W \rightarrow W_\eta^-$ if $w_\eta < k$;

- (iv) $R_\eta(W)$ and $q_\eta(W)$ depend continuously on $\eta \in [0, 1]$ if $1 < W < W_\eta$; in addition, w_η depends continuously on $\eta \in [0, 1]$.

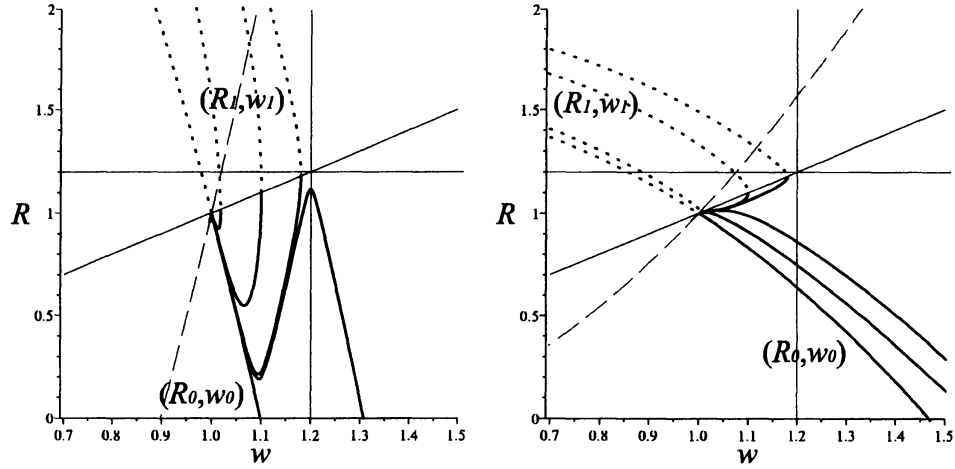


Figure 5: Projection of curves on the local stable manifold onto (R, W) -space (with $\gamma = 1$, $k = 1.2$); (left) the case $c = 0.3$, (right) the case $c = 0.5$. The dashed curve corresponds to a unstable manifold.

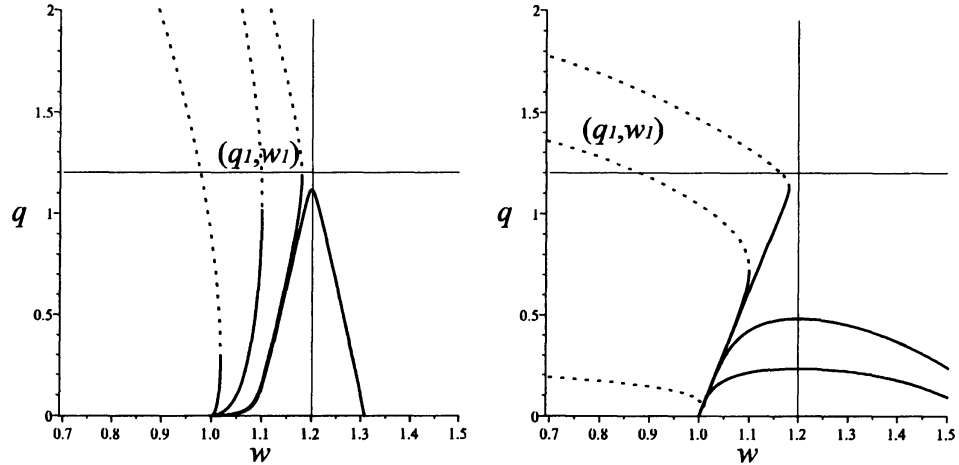


Figure 6: Projection of curves on the local stable manifold onto (q, W) -space (with $\gamma = 1$, $k = 1.2$); (left) the case $c = 0.3$, (right) the case $c = 0.5$.

Sketch of proof of Theorem 2. We define

$$E_- := \{\eta \in (0, 1); W_\eta = k\}$$

and

$$E_+ := \{\eta \in (0, 1); W_\eta \in (1, k] \text{ and } R_\eta(W) - W \rightarrow 0 \text{ as } W \rightarrow W_\eta^-\}.$$

It follows from properties (ii) and (iv) of Lemma 3.5 that $E_+ \neq \emptyset$. Moreover, it can be proved by a contradiction that if $c > c_0$, then $E_- \neq \emptyset$. In addition they are closed in the

relative topology of $(0, 1)$: the complementary sets in $(0, 1)$ are open, since R_η depends continuously on η . Since $E_+ \cup E_- = (0, 1)$, there exists $\bar{\eta} \in E_+ \cap E_-$. It follows from the definition of E_\pm that

$$w - R_{\bar{\eta}}(w) > 0 \text{ in } [1, k) \quad \text{and} \quad R_{\bar{\eta}}(w) \rightarrow k \text{ as } w \rightarrow k^-.$$

Finally, it is proved that $(R_{\bar{\eta}}, q_{\bar{\eta}})$ is a solution of the problem. We will prove that for $c > c_0$ there exists solution of the problem

$$\begin{cases} R_W = \frac{-kW^2(W-1)R + W^2(k(W-1) + \gamma(k-W))q}{c^2kR(W-R)} \\ q_W = \frac{\gamma W^2(k-W)q}{c^2kR(W-R)} \\ R(1) = 1, \quad q(1) = 0, \quad R(k) = q(k) = k \end{cases}$$

and

$$q(W) > 0 \quad \text{in } (1, k).$$

Thus it completes a proof. □

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